

FASCIOTOMY REDUCES COMPARTMENT PRESSURES AND IMPROVES RECOVERY IN A
PORCINE MODEL OF EXTREMITY VASCULAR INJURY AND ISCHEMIA/REPERFUSION

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Objective: The objective of this study is to establish a model of extremity compartment syndrome following vascular injury, hemorrhage and ischemia/ reperfusion. An additional objective is to determine the effect of fasciotomy on measures of neuromuscular recovery.

Methods: Yorkshire swine (75+/-5kg) underwent 35% blood volume hemorrhage, followed by 1, 3 and 6 hours of ischemia (n=17; 1HR, 3HR, 6HR) via iliac artery occlusion followed by repair and reperfusion. A second cohort (n=18) underwent fasciotomy of the anterior compartment of the hind limb following vascular repair (1HR-F, 3HR-F, 6HR-F). Compartment pressures and measures of electromyographic (EMG) recovery were performed throughout a 14 day survival period and tissue histology examined at the completion of the study.

Results: Increasing ischemic intervals resulted in incremental increases in compartment pressure ($p<0.05$) which were directly related to degree of muscle degeneration ($p<0.05$) and inversely related to nerve recovery ($p<0.05$). Fasciotomy prevented increases in compartment pressure ($p<0.05$) and improved nerve recovery in the 3HR-F but not the 6HR-F group. Fasciotomy following 6 hours of ischemia (6HR-F) resulted in apparent decreases in muscle degeneration ($p=.15$).

Conclusion: This study demonstrates a model of vascular injury, hemorrhage and compartment syndrome supporting the effectiveness of prophylactic fasciotomy. In this model, elevated compartment pressures limit nerve recovery following extremity vascular injury; a negative effect which is mitigated by fasciotomy in conjunction with restoration of flow within 3 hours of injury.

Introduction

Extremity vascular trauma represents 75-88% of vascular injury in wars in Iraq and Afghanistan^{i, ii} with limb salvage from these wars approaching 80%.^{iii, iv} In World War II, the Korean War and Vietnam the amputation rates were 44%, 13% and 13.5% respectively.^{v, vi, vii} Injured soldiers were not given an opportunity for limb salvage due to prolonged time ischemic time. During Iraq and Afghanistan the time to surgical treatment has decreased to approximately 60 minutes, decreasing the ischemic interval and improving the probability for functional limb salvage.^{viii}

Functional limb salvage is maximized with early restoration of flow and mitigating the secondary effects of reperfusion injury. Early restoration of flow has been achieved with forward deployment of surgical units and utilization of temporary vascular shunts.^{ix} Reperfusion injury decreases functional outcome through many mechanisms to include the development compartment syndrome, which is treated with fasciotomy. Timing of fasciotomy is critical to improved limb salvage, with prophylactic fasciotomy the best opportunity for limb salvage.^x The number of fasciotomies during the most recent wars has increased due to improved awareness.^{xi} The benefit of fasciotomy has been proven to decrease amputation rates and improve limb salvage but it is difficult to quantify the improvement in functional recovery after defined ischemic intervals. This question can only be answered through the use of animal models.

Large animal research models evaluating ischemia/reperfusion injury and compartment syndrome have been successful in non-survival animal models to show that fasciotomy improved muscular contraction in comparison with mannitol or super oxide dismutase.^{xii} Currently there

are few studies evaluating the long term outcomes of limb ischemia/reperfusion. Recently our group developed a porcine model of hind limb ischemia that shows the functional recovery through neuromuscular recovery of swine over a two week period.^{xiii} The initial experiment developed a model of hind limb ischemia that defined the ischemic threshold to be between three and six hours.^{xiv} In the following model, a 35% blood volume hemorrhage was added and the ischemic threshold was shifted between one and three hours.^{xv} These studies set the ischemic thresholds and baselines for neuromuscular recovery after varying hours of ischemia. To date, no large animal models of ischemia/reperfusion injury have quantified neuromuscular recovery of prophylactic fasciotomy after varying hours of ischemia.

Fasciotomy is the standard of care for improving functional limb outcome by reducing the effect of compartment syndrome caused by ischemia/reperfusion injury.^{xvi} The objective of this study is to establish a model of extremity compartment syndrome following vascular injury, hemorrhage and ischemia/reperfusion. Additional objectives include determination of the effect of fasciotomy on measures of neuromuscular recovery, laboratory evaluation and histology. Our hypothesis is that prophylactic fasciotomy will help preserve limb function and improve neuromuscular recovery in comparison with the non-fasciotomy groups.

Methods

Protocol Phase

Institutional Animal Care and Use (IACUC) review and approval of this protocol was obtained. All procedures and operative studies were performed at United States Army Institute of Surgical Research at Fort Sam Houston, Texas which is an accredited animal research facility.

All IACUC policies were followed and the care of the animals was under the supervision of a licensed veterinarian.

Group Definition

Forty female yorkshire ($75 \pm 5\text{kg}$) swine (Sus Scrofa; Midwest Research Swine, 31009 645th Ave., Gibbon, MN 55335) were housed 7 days prior to the initiation of the protocol for an acclimation and observation period. On the day of surgery, the swine were randomized to 1, 3 or 6 hours of ischemia without fasciotomy (1HR, 3HR, 6HR) or 1, 3 or 6 hours of ischemia with fasciotomy (1HR-F, 3HR-F, 6HR-F).

Operative Phase

Induction of anesthesia was performed with ketamine (15-20mg/kg) and atropine (0.04-0.4mg/kg) intramuscularly with maintenance of anesthesia with 2-4% isoflurane in an air-oxygen mixture of 40 to 60% by facemask until endotracheal intubation was performed. The animal was then placed in the supine position on the operating table. The neck, abdomen and right lower extremity were then shaved. Pre-operative studies were performed and will be described. The neck, abdomen and right limb were then prepped with povidine-iodine, and draped. A midline incision was made over the trachea, with dissection through the midline connective tissue of the strap muscles. Blunt and sharp dissection was used to expose the right internal jugular vein and internal carotid artery. Both were cannulated after distal ligation with an 8F Cordis for resuscitation and blood pressure monitoring respectively. A 10 milliliter arterial blood sample was sent for circulating biomarkers. The wound was packed with moist laps and left open throughout the remainder of the case. A low abdominal midline incision from the pubic symphysis to the second or third inferior nipple was made. A retroperitoneal approach was used to expose a 5 - 6cm segment of the right external iliac artery. This was exposed to the external

iliac bifurcation. Vessel loops were placed proximally around the right external iliac artery and distal around the branches of the external iliac arteries. The distal vessel loops were tightened which initiated the start of the ischemic time. The right external iliac artery was cannulated with an 8F Cordis.

Hemorrhage, Shock and Resuscitation Phase

A 35% variable rate hemorrhage, 1.6cc/kg/min for 7 minutes then 0.85cc/kg/min for 13 minutes^{xvii} through the right external iliac artery. This was performed using with a Masterflex Easy Load II peristaltic rotary infusion pump with computerized drive (Cole-Parmer Instrument Co., Vernon Hills, Ill) using customized LabVIEW software (National Instruments Corp, Austin, Tex). Calibration of the system was performed the morning of each surgical procedure. The right external iliac catheter was removed after completion of the hemorrhage period. After a 30 minute shock period, shed blood resuscitation and maintenance normal saline infusion at 150cc/hr was then initiated to restore the mean arterial pressure to > 60mm Hg. If the animal remained hemodynamically labile after utilization of the shed blood, normal saline boluses were given in 500cc aliquots.

Arterial Repair

After the assigned ischemic interval of 1, 3 or 6 hours, restoration of flow was performed by Dacron patch angioplasty. The puncture wound from insertion of the 8F Cordis was extended proximally and distally for an incision size of approximately 2-4 cm. Antegrade and retrograde bleeding was performed. If there was poor retrograde bleeding a thrombectomy was performed with a 2F fogarty catheter, a maximum of three passes was performed. Regional heparinization (1unit/milliliter) was used during the repair. Confirmation of flow through the patch was

confirmed using Doppler probe. If the patch was found to be occluded at time of operative repair, the patch was opened, thrombectomy was performed and patch angioplasty was repeated.

Fasciotomy

Prophylactic fasciotomy of the anterior compartment was performed at the time of restoration of flow. An 8 – 10 cm longitudinal incision was made over the anterior compartment exposing the fascial compartment (Fig 1). After the fascial compartment was opened the muscle belly was detached from the bone to ensure adequate compartment release. A Jacobs ladder was then created with packing of two 4x4 pieces of moist gauze in the open wound (Fig 1). On post-operative day number one the fasciotomy site was irrigated and scrubbed with a Hibiclens scrub brush. The wound was closed with 2-0 prolene in a vertical mattress fashion. It was monitored on pre-determined post-operative days for signs of infection.

Miscellaneous

All animals remained with an open abdomen and neck for approximately 7 hours. At the conclusion of the experiment, the abdomen and neck were closed in layers using O-Vicryl sutures and #1 PDS. Skin was closed with staples.

During the operative procedure, continuous measurement of vital signs (heart rate, blood pressure, temperature, urine output), end tidal CO₂ and oxygen saturation were monitored.

For pain control the animals had a fentanyl patch (25mcg/hr) placed prior to surgery protocol and received buprenorphine 0.01-0.05 mg/kg SQ if they were deemed to have increased post-operative pain as determined by the veterinarian. Aspirin (81mg) and Rocephin (1 gm twice a day) were given throughout the study period.

Follow Up Period

Post-operative studies were performed on postoperative day 1, 2, 7 and 14. Induction of anesthesia was performed with ketamine (15-20mg/kg) and atropine (0.04-0.4mg/kg) intramuscularly with maintenance of Isoflurane 2-4% in by an air-oxygen mixture of 40 to 60% by facemask. On post-operative day 14 the animals were endotracheally intubated prior to the studies being performed.

Compartment Pressure Measurement

Anterior compartment pressures were evaluated using Stryker Intra-Compartmental Pressure Monitor (Kalamazoo, MI) were checked bilaterally in the anterior compartment. The device was primed, zeroed and inserted into the anterior compartment. A 0.5 milliliter injection of normal saline was performed and the monitor was allowed to equilibrate with the pressure being recorded. The measurement was obtained three times in each limb. Compartment pressures checked post-operatively on the fasciotomy group compartment were performed in the exposed muscle belly. On post-operative day 1 the compartment pressure was checked after closure of the wound.

Functional limb outcome

Limb function was evaluated by nerve conduction studies (Compound Motor Action Potential (CMAP), Sensory Nerve Action Potential (SNAP) and Nerve Conduction Velocity (NCV) and gait testing. CMAP was obtained by stimulation of the peroneal nerve with external sensors placed over the anterior compartment muscle belly and knee. SNAP was collected by stimulation of the mixed tibial nerve at the foot with subcutaneous needles placed at fixed distances. Each nerve conduction study was consistently reproduced three times by a single user. Spot checks of waveforms were performed by a board certified neurologist.

Flow Velocity Measurement

Flow velocity through the right and left common femoral arteries were performed pre-operatively and on the defined post-operative intervals.

Circulating Biomarkers

Circulating biomarkers include Na, K, Cl, CO₂, BUN, Creatinine and Glucose.

Circulating markers ischemia include LDH, CK, Lactate and Myoglobin. Other labs include AST, CBC and ABG. All lab samples were arterial blood draws from either the right internal carotid artery or a superficial arterial stick on the hind limb.

Histology

On post-operative day 14, necropsy was performed in a standardized fashion with harvesting of the peroneus tertius muscle and peroneal nerve of the anterior compartment. The complete peroneus tertius muscle was harvested and cut into three equal sections with the distal section being used for weight to dry calculations. The middle third of peroneus tertius muscle and the peroneal nerve were placed in formalin, stained with hematoxylin and eosin and Masson's Trichrome which was evaluated by the veterinary pathologist. Variables for the peroneal evaluation included nerve degeneration and nerve inflammation. The peroneus tertius muscle was evaluated for degeneration, inflammation and fibrosis (Table 1).

Statistical Analysis

The sample size of 6 per group provides 80% power to detect an effect size of 0.6 (or 213 approximately 1.2 stdev difference among means) for the main factor of group, 0.42 (or 214 approximately 0.84 stdev difference across time, and an effect size of 0.6 for the interaction term 215 between group and time when testing with a repeated measures ANOVA (with 6 groups) at the alpha level of 0.05. Differences larger than 1.2 stdev are anticipated especially with the 6 hour delay to reperfusion group.

Statistical analysis was completed using SAS 9.2 Software (SAS Institute, Cary, NC) and Microsoft Excel (Microsoft, Redmond, Washington, USA). One way ANOVA was used to calculate a difference among means for quantitative measures. Post-hoc T-tests were performed if significance was identified among groups to identify the statistical difference between the groups. Wilcoxon Mann/Whitney U tests were used for comparison of histopathologic differences.

The physiologic model of recovery was calculated by combining the individual difference of CMAP, SNAP and NCV in equal proportions. Each individual animal variable was compared from the time points of immediately post-op, POD1, POD2, POD7 and POD14 to baseline. Combination of the percent change from the individual components comprises the PMR. The PMR was then evaluated by one way ANOVA with post hoc t-test.

Results

Baseline Characteristics

No statistical differences were demonstrated between neuromuscular and hemodynamic variables (Table 2). 43 animals entered the study, with three animals for model development and five of those animals being replaced due to premature death. All five animals expired within the first 24 hours, the cause was deemed to be cardiopulmonary failure secondary to disseminated intravascular coagulopathy (3 in the 3HR, 2 in the 3HR-F).

Circulating Biomarkers

At the conclusion of the 14 day study period, no statistical difference was found between study groups. Ischemic laboratory markers (K, myoglobin and creatinine phosphokinase) between the fasciotomy and no fasciotomy groups at 1, 3 and 6 hours of ischemia did not have statistical significance (Table 3).

Flows

On post operative day 14 a statistical difference between 3HR and 3HR-F (68cm/s v. 45cm/s, $p=0.04$) was identified. No remaining statistical differences were identified on POD14. All flow rates returned to baseline values (Table 3).

Compartment Pressure

An incremental increase in compartment pressure was seen among the non-fasciotomy group. Comparing the groups, 6HR had the greatest increase in comparison with 1HR and 3HR ($p<0.0001$, $p<0.0001$ respectively). The greatest difference in compartment pressure was seen on POD1 (6HR 27.4 ± 3.6 mmHg, 3HR 10.3 ± 2.4 mm Hg, 1HR 10 ± 1.2 mm Hg; 6HR v. 3HR $p<0.0001$, 6HR v. 1HR $p<0.0001$). The statistical difference between compartment pressures comparing the 6HR v. 3HR and 1HR persisted until POD7 ($p=0.040$, $p<0.0003$). All compartment pressures returned to normal by POD14 (Graph 1).

Comparing compartment pressures for the 1HR-F, 3HR-F and 6HR-F, a statistical difference comparing group means was found between 6HR-F v. 1HR-F and 3HR-F ($p=0.028$, $p=0.047$). Individual time comparison among groups did not yield a statistical difference (Graph 1).

At 1 hour of ischemia between the 1HR v. 1HR-F groups, no statistical difference was found ($p=0.56$). 3 Hours of ischemia had a difference among means ($p=0.0081$), further analysis on POD7 found 3HR to have a significantly higher pressure (3HR 15.3mm Hg, 3HR-F 7.2; $p=0.009$).

At six hours of ischemia, a significant difference was found between 6HR and 6HR-F ($p<0.0001$) with 6HR having significantly increased compartment pressures from the post-operative time point through POD7. POD2 had the greatest difference in compartment pressures

(6HR 25.3 ± 3.2 mm Hg, 6HR-F 11.9 ± 1.5 mm Hg; $p < 0.0002$). On POD14 no difference was noted.

Neuromuscular Recovery

CMAP

Comparison among the non-fasciotomy groups revealed a statistical difference among the groups ($p < 0.05$). At day 14 a statistical difference between 1HR compared with 3HR and 6HR (1HR 10.3 ± 1.0 mV, 3HR 5.9 ± 1.5 mV, 6HR 3.2 ± 1.4 mV; $p = 0.0027$, $p < 0.0001$; respectively). No difference was identified between 3HR and 6HR ($p = 0.1068$).

Comparing the fasciotomy group at day 14, no difference was identified between 1HR-F and 3HR-F. A significant difference between the 6HR-F compared with 1HR-F and 3HR-F (1HR-F 4.5 ± 0.3 mV, 3HR-F 4.9 ± 1.3 mV, 6HR-F 1.6 ± 0.7 mV; $p = 0.0363$, $p = 0.0255$; respectively).

Comparison between the fasciotomy and non-fasciotomy groups at the given ischemic intervals had a statistical difference at 1 hour (1HR 10.3 ± 1.0 mV, 1HR-F 4.5 ± 0.3 mV; $p = 0.0007$). No difference was identified between 3HR and 3HR-F or 6HR and 6HR-F.

SNAP

At POD14, there was a statistically significant decrease when the comparing 1HR to 3HR and 6HR (1HR 14.9 ± 2.1 uV, 3HR 8.1 ± 1.5 uV, 6HR 5.0 ± 0.9 uV; $p = 0.0035$, $p < 0.0001$; respectively). There was no statistical difference comparing 3HR-F to 6HR-F.

In the fasciotomy groups, SNAP was statistically different when comparing 6HR-F to 1HR-F and 3HR-F (1HR-F 11.5 ± 1.0 , 3HR-F 11.3 ± 1.1 , 6HR-F 5.1 ± 1.4 ; $p = 0.0098$, $p = 0.039$; respectively). There was no statistical difference between 1HR-F and 3HR-F.

On POD14, there was no difference between the groups at 1, 3 and 6 hours of ischemia.

NCV

No statistical difference was identified among group comparison.

PMR

There was a stepwise decrease in neuromuscular recovery with increasing intervals of ischemia (1HR $3.08 \pm 5\%$, 3HR $34.2 \pm 9\%$, 6HR $53\% \pm 7.5\%$). The statistically significant difference between 1HR compared with 3HR and 6HR ($p=0.0067$; $p<0.0001$) with no statistical difference when comparing the 3HR and 6HR groups ($p=0.12$).

An increase in the severity of neuromuscular recovery was also found in the fasciotomy groups (1HR-F $14.8 \pm 7.8\%$, 3HR-F $19 \pm 9.3\%$, 6HR-F $48.6 \pm 10.6\%$). No statistical difference was found between the 1HR-F and 3HR-F ($p=0.96$) but comparing the 6HR-F to 1HR-F and 3HR-F a difference was noted ($p=0.0042$; $p=0.0036$).

There was no difference between 1HR v 1HR-F, 3HR v 3H-F and 6HR v 6HR-F. There was an apparent improvement in neuromuscular recovery in the 3 hour ischemia groups with 3HR-F having $19 \pm 9.3\%$ loss and 3HR having $34.2 \pm 9.0\%$ loss ($p=0.0982$).

Histopathology

The non-fasciotomy groups had an increasing amount of muscle degeneration, inflammation and fibrosis with increasing intervals of ischemia. A statistical difference was noted between 1HR and 6HR with regards to muscle degeneration and muscle fibrosis ($p=0.0156$; $p=0.0065$; respectively). Nerve degeneration and inflammation did not have a stepwise increase in grading as the 3HR animals had the worst nerve damage. A statistical difference was identified when comparing nerve inflammation between the 1HR in comparison with 3HR and 6HR ($p=0.040$; $p=0.008$). When comparing nerve degeneration a difference was identified between the 1HR and 6HR groups ($p=0.027$).

No difference among groups in the fasciotomy animals was identified.

When comparing the animals at individual time intervals, there was a statistically significant difference comparing 1HR and 1HR-F across all categories with the 1HR-F having increased fibrosis, necrosis and degeneration. No other differences were identified comparing the 3 hour ischemia groups and the 6 hour ischemia groups (Table 3).

Discussion

This study demonstrates a reproducible model of vascular injury, hemorrhage and compartment syndrome supporting the effectiveness of prophylactic fasciotomy. In this model, increases in compartment pressure were recorded with increasing length of ischemia. The increased length of ischemia resulted in worsened neuromuscular recovery that was confirmed with histologic evaluation. Fasciotomy successfully relieved increased compartment pressure at the 3 and 6 hours of ischemia. At 6 hours fasciotomy did not improve neuromuscular recovery but at 3 hours of ischemia trend toward recovery was identified. This suggests that with fasciotomy, the optimal time for improved neuromuscular recovery is between one and three hours.

The most effective way for improving neuromuscular recovery is early restoration of flow. During WWII, amputation rates increased as the time to restoration of flow took place.^{xviii} As the time to surgical repair decreased to less than 60 minutes, as in Iraq and Afghanistan, the opportunity to mitigate ischemic damage improved.^{xix} Temporary vascular shunts are a widely used adjunct currently to decrease the ischemic interval while other injuries are being addressed or the patient can be transferred to a higher level of care.^{xxxxi} A large animal model revealed that a shunt placed in less than three hours from injury had a lower circulating ischemia index, with good shunt patency over 18 hours.^{xxii} A short term canine study showed the animals that

received prophylactic fasciotomy were found to have normal muscle contraction in comparison with the mannitol or superoxide dismutase group.^{xxiii}

To date, only two studies have been performed evaluating the long term neuromuscular recovery of various ischemic intervals in a large animal model. The initial study performed by our group evaluated the effect of ischemia reperfusion in the absence of hemorrhage and without intervention. It was determined the ideal interval for limb reperfusion was between 3 and 6 hours..^{xxiv, xxv} The next study evaluated the effect of ischemia reperfusion in the presence of a 35% blood volume hemorrhage with a 30 minute shock period. The ideal time for reperfusion in the presence of hemorrhage revealed the interval to be less than three hours.^{xxvi}

The current study confirmed the results of Hancock et. al. that in the presence of hemorrhage there is not a statistical difference between the three and six hour ischemia groups in the presence of 35% blood volume hemorrhage. The addition of fasciotomy decreased revealed a statistical difference between three and six hour ischemia groups, significantly improving their neuromuscular recovery.

In a large animal survival model, fasciotomy was shown to improve the functional neuromuscular outcome of the injured limb. This confirms the current practice guidelines from the current wars in Iraq and Afghanistan. In the early portions of the wars, if patients did not received delayed fasciotomies, there were higher rates of muscle excision, amputation and mortality than those patients who received prophylactic fasciotomies.^{xxvii}

Limitations of this study include the inability to complete release all compartments of the lower extremity in a swine. The circulating biomarkers did not show a significant difference due to the limitation. The anterior compartment was the selected compartment for release due to its containment of the nerves being tested for the PMR. Another limitation of the histologic

evaluation of the specimens in the fasciotomy groups. With release of the compartments and blunt dissection of the muscle off of the bone, there was baseline inflammation and fibrosis that would take place, independent of the ischemic interval. This variable could not be controlled for. Lastly, measures of neuromuscular recovery were decreased in the fasciotomy group secondary to seroma formation in the released compartment. The relatively short shock period of 30 minutes and the resuscitation with whole blood is not representative of current clinical practice.

Conclusion

In the presence of class III hemorrhagic shock, prophylactic fasciotomy improves neuromuscular recovery at 3 hours of ischemia in comparison with the non-fasciotomy group. Early restoration of flow, less than one hour, should be instituted in order to maximize neuromuscular recovery. The ideal time for prophylactic fasciotomy is one and three hours.

Figure 1.



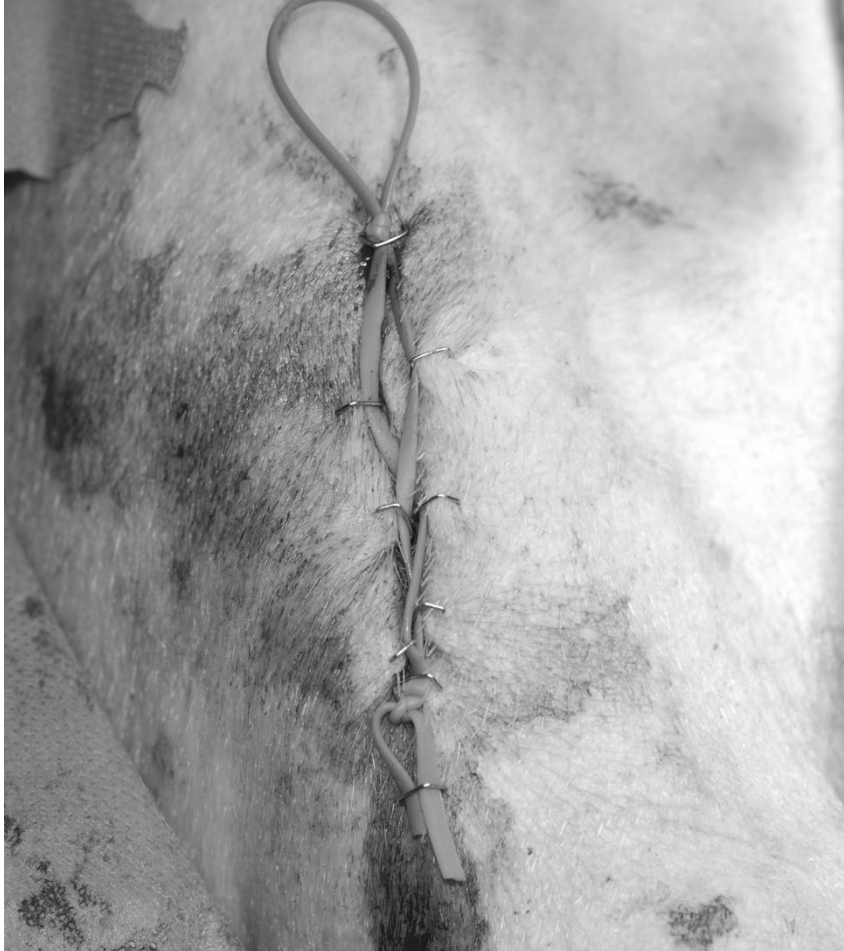


Figure 1. Fasciotomy site from the distal to the knee to the ankle. Closed with a Jacobs ladder.

Table 1.

Score	Peroneus Tertius Muscle	Peroneal Nerve Degeneration	Peroneal Nerve Inflammation
0	No Involvement	No Involvement	No Involvement
1	1%-25% cross-sectional area	Mild	Minimal
2	26%-50% cross sectional area	Moderate	Mild
3	51%-75% cross sectional area	Severe	Moderate
4	76%-100% cross sectional area		Severe

Table 1. Pathology Grading system.

Table 2.

<i>Variable, Means (SD)</i>	<i>1 HR</i>	<i>1 HR-F</i>	<i>3 HR</i>	<i>3 HR-F</i>	<i>6 HR</i>	<i>6 HR-F</i>	<i>P</i> <i>Value</i>
	<i>n = 6</i>	<i>n = 6</i>	<i>n = 5</i>	<i>n = 6</i>	<i>n = 6</i>	<i>n = 6</i>	
Weight, kg	76.5 (3.0)	73.7 (8.8)	76.2 (3.3)	76.6 (76.4)	73.8 (7.0)	77.9 (4.0)	0.78
Mean arterial pressure, mm Hg	72 (6.3)	60 (10.4)	70 (18.5)	66 (10.4)	54 (15.2)	63 (17.8)	0.28
Hemoglobin, g/dl	10.2 (0.9)	10 (0.9)	9.6 (1.1)	9.7 (0.7)	9.4 (0.8)	9.8 (0.6)	0.68
Compartment Pressure, mm Hg	9.0 (1.7)	8.8 (2.4)	10.4 (2.2)	9.2 (4.2)	8.2 (2.3)	8.7 (2.1)	0.82
Aspartate aminotransferase, IU/L	29 (12.6)	26 (7.4)	29 (13.7)	23 (2.7)	27 (4.2)	28 (9.1)	0.88
Lactate, U/L	1.1 (0.6)	1.3 (0.3)	1.7 (1.0)	1.3 (0.5)	1.2 (0.6)	1.7 (0.8)	0.5
Creatinine phosphokinase, ug/L	1548 (2248)	807 (400)	1272 (964)	636 (164)	1009 (651)	688 (182)	0.51
Potassium, mEq/L	3.9 (0.3)	4.0 (0.3)	4.3 (1.0)	3.9 (0.3)	3.8 (0.3)	4.1 (0.4)	0.6
Myoglobin, ng/mL	47 (27.6)	49.3 (36.5)	38 (17.0)	40 (17.5)	26 (5.1)	46 (18.9)	0.41
Lactate Dehydrogenase, U/L	298 (170)	301 (143)	341 (74)	275 (70)	228 (97)	248 (86)	0.49
Complex motor action potential, mV	12.5 (2.2)	9.3 (1.7)	13.3 (3.7)	10.2 (2.3)	12.3 (2.3)	9.8 (3.0)	0.07
Sensory nerve action potential, uV	14.5 (3.9)	13.3 (2.9)	13.4 (3.6)	14.9 (3.3)	12.4 (1.7)	11.0 (3.4)	0.35
Nerve Conduction Velocity, m/s	57.8 (6.7)	56.4 (7.4)	58.2 (7.1)	56.8 (7.6)	60.7 (7.2)	55.4 (7.3)	0.86
Common femoral artery velocity, cm/sec	54.3 (8.0)	63.2 (13)	49.1 (9.5)	55.9 (15.3)	56.0 (18.8)	58.8 (13.4)	0.66

Table 2. Baseline Characteristics. No statistical difference among groups was identified.

Table 3.

<i>Variable, Means ± SE</i>	<i>1 HR n = 6</i>	<i>1 HR-F n = 6</i>	<i>3 HR n = 5</i>	<i>3 HR-F n = 6</i>	<i>6 HR n = 6</i>	<i>6 HR-F n = 6</i>	<i>P Value</i>
Hemoglobin, g/dl	12.4 ± 0.2	10.7 ± 0.3	11.7 ± 0.6	10.7 ± 0.4	10.9 ± 0.6	10.1 ± 0.3	0.1942
Compartment Pressure, mm Hg	8.7 ± 1.0	7.8 ± 1.8	11.6 ± 1.0	9.2 ± 1.9	10.4 ± 3.9	11.8 ± 4.9	<0.0001 ^a
Aspartate aminotransferase, IU/L	44 ± 6.3	50 ± 8.0	45 ± 4.0	45 ± 8.6	52 ± 3.6	50 ± 5.9	0.8233
Lactate, U/L	1.3 ± 0.2	2.5 ± 1.0	1.4 ± 0.5	2.2 ± 0.8	2.8 ± 0.9	1.9 ± 0.5	0.1687
Creatinine phosphokinase, ug/L	2230 ± 684	2186 ± 594	2522 ± 575	1552 ± 788	2159 ± 412	2617 ± 322	0.6743
Potassium, mEq/L	3.8 ± 0.1	3.6 ± 0.1	3.8 ± 0.1	3.7 ± 0.2	3.8 ± 0.3	3.7 ± 0.2	0.1434
Myoglobin, ng/mL	63 ± 31.9	48 ± 8.7	39 ± 7.3	23 ± 6.9	39 ± 6.5	22 ± 2.2	0.4584
Lactate Dehydrogenase, U/L	519 ± 50.8	647 ± 99.0	727 ± 128.0	567 ± 122.1	684 ± 73.9	606 ± 97.7	0.4688
Complex motor action potential, mV	10.3 ± 1.0	4.5 ± 0.3	5.9 ± 1.5	4.9 ± 1.3	3.2 ± 1.4	1.6 ± 0.7	<0.0001 ^b
Sensory nerve action potential, uV	14.9 ± 2.1	11.5 ± 1.0	8.1 ± 1.5	11.3 ± 1.1	5.0 ± 0.9	5.1 ± 1.4	<0.0001 ^c
Common femoral artery velocity, cm/sec	59.8 ± 5.1	64.2 ± 10.6	68.3 ± 6.3	44.5 ± 7.8	61.1 ± 6.8	65.1 ± 5.4	0.0141 ^d

Table 3. Final Characteristics at post-operative day 14.

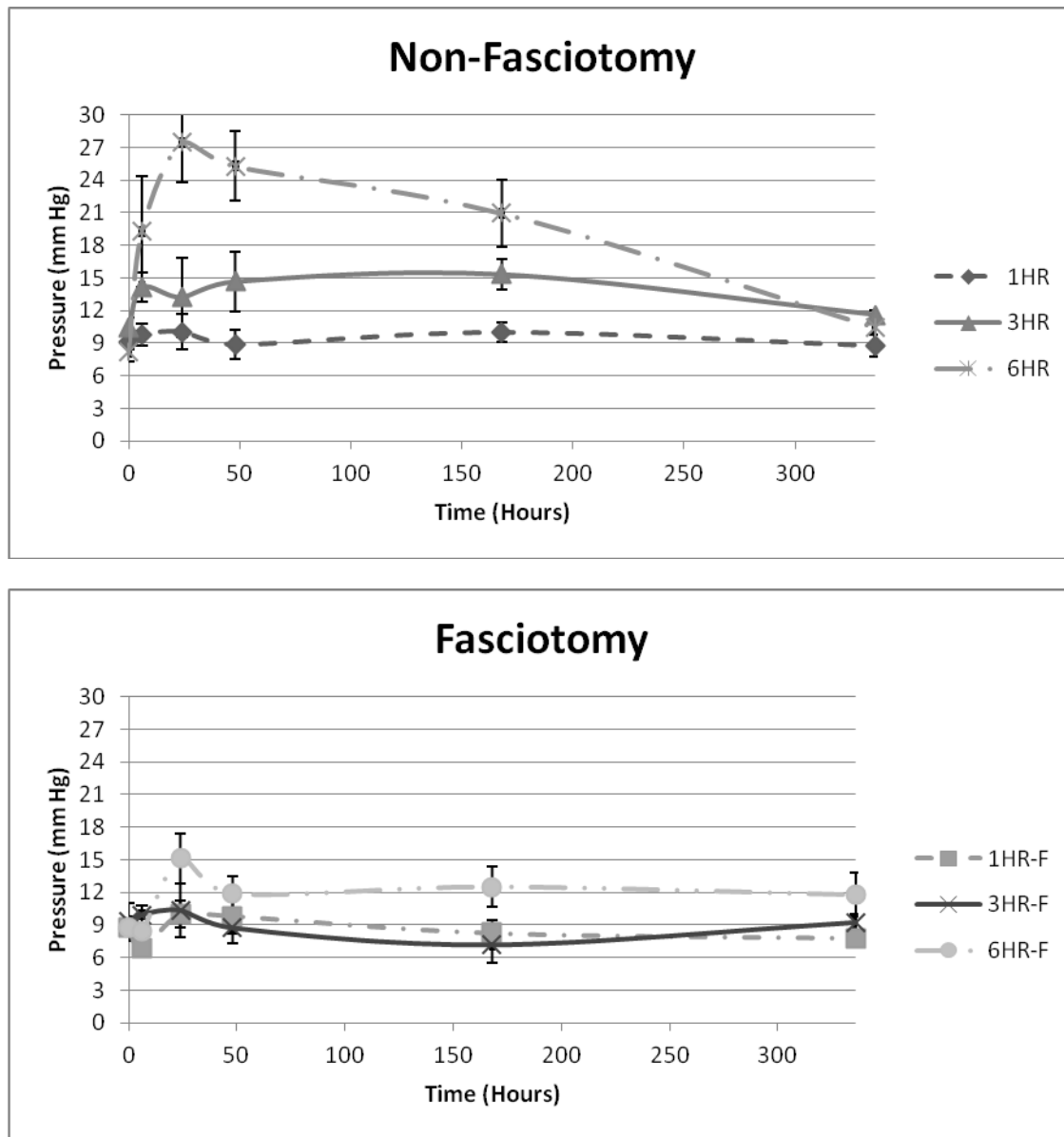
^a Post-hoc analysis did not reveal a statistical difference on day 14.

^b Post-hoc analysis revealed a statistical difference between 1HR compared with 3HR and 6HR for the non-fasciotomy groups. There was a significant difference when comparing 6HR-F with 1HR-F and 3HR-F.

^c A statistical difference remained with comparing 1HR to 3HR and 6HR for the non-fasciotomy groups. When comparing the fasciotomy groups a difference was present comparing 6HR-F to 1HR-F and 3HR-F.

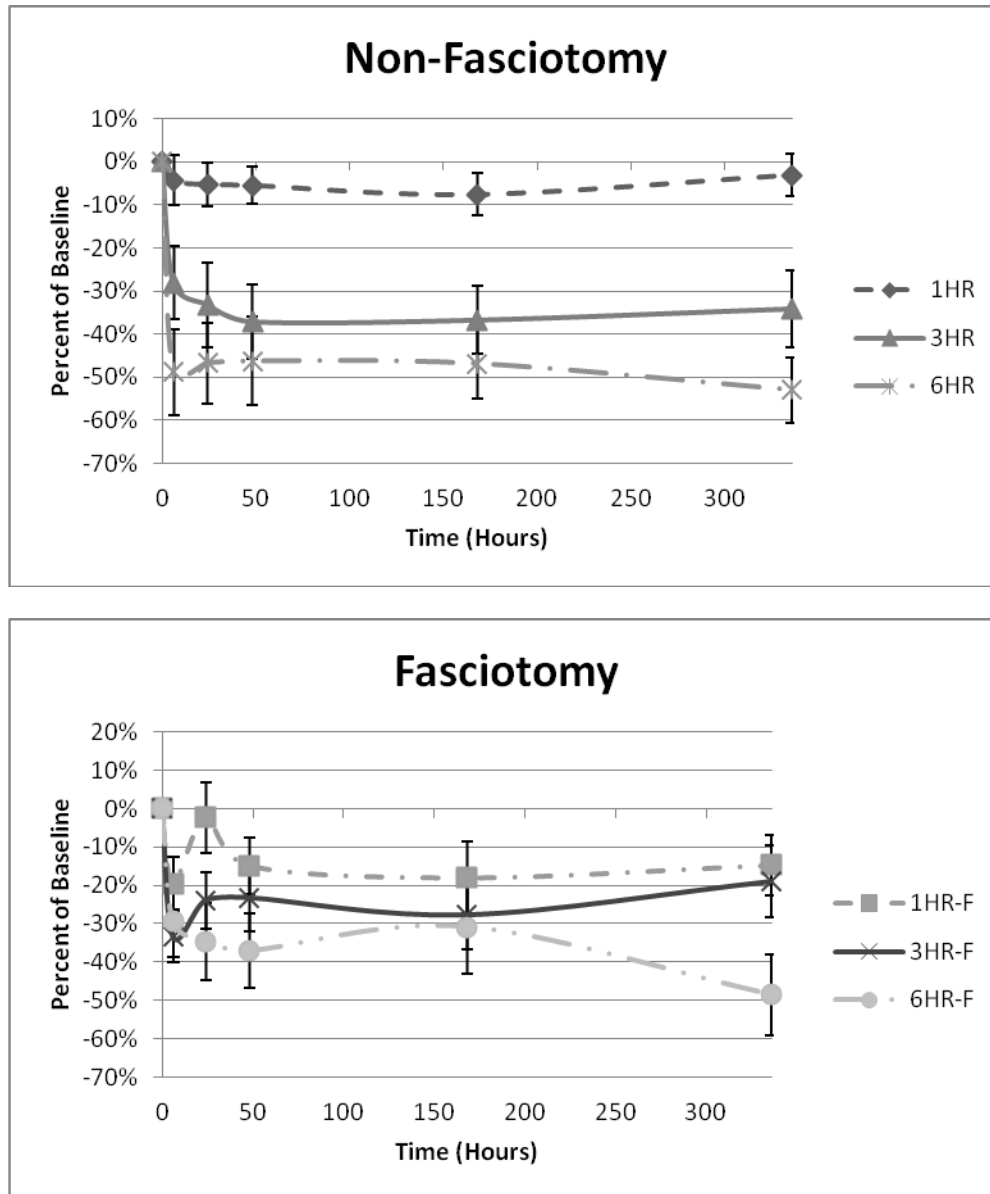
^d At day 14 no difference was identified between individual groups.

Graph 1.



Graph 1. Compartment Pressure. The non-fasciotomy groups had a step wise increase in compartment pressure with the lengthening of ischemia. Statistically significant differences were present when comparing the 1HR to 3HR and 6HR at 24 hours through 7days. This difference resolved by day 14. The fasciotomy groups did not a statistically significant difference when comparing compartment pressure at individual time points. Comparison between groups showed significant difference in compartment pressure between 6HR and 6HR-F that started at 6 hours and persisted until day 7. 3HR and 3HR-F had a significant difference at day 7.

Graph 2.



Graph 2. Physiologic Model of Recovery. The fasciotomy group showed a statistical difference on day 14 comparing the 1HR to the 3HR and 6HR. There was no difference between the 3HR and 6HR. When comparing the fasciotomy groups, there was a statistical difference between the 6HR-F compared with 3HR-F and 1HR-F. When the individual time comparisons were performed no difference was identified.

Table 3.

<i>Characteristic</i>	<i>1HR</i>	<i>3HR</i>	<i>6HR</i>	<i>1HR-F</i>	<i>3HR-F</i>	<i>6HR-F</i>	<i>P Value</i>
<i>Mean ± SE</i>							
Nerve							
Degeneration	0.67 ± 0.21	2.0 ± 0.71	1.8 ± 0.37	1.6 ± 0.22	1.67 ± 0.42	2.0 ± 0.45	0.17
Inflammation	0.17 ± 0.17	1.75 ± 0.63	1.6 ± 0.40	0.80 ± 0.18	1.67 ± 0.42	1.2 ± 0.37	0.03 ^a
Muscle							
Degeneration	0.67 ± 0.21	1.6 ± 0.60	2.83 ± 0.60	1.5 ± 0.50	1.83 ± 0.4	1.67 ± 0.33	0.05
Inflammation	0.67 ± 0.33	1.4 ± 0.75	2.67 ± 0.61	1.33 ± 0.33	1.83 ± 0.54	1.5 ± 0.5	0.23
Fibrosis	0.50 ± 0.22	1.6 ± 0.4	2.83 ± 0.48	1.33 ± 0.33	2.0 ± 0.45	1.8 ± 0.40	0.012 ^b
Wet-Dry Ratio	4.0 ± 0.28	4.14 ± 0.58	4.56 ± 0.47	4.53 ± 0.12	4.4 ± 0.21	4.63 ± 0.14	0.31

Table 3. Pathology Results

^a Post-hoc analysis revealed a difference between 1HR when compared with 3HR and 6HR. The fasciotomy groups had a difference between 1HR-F and 3HR-F. Intergroup comparison revealed a difference between 1HR and 1HR-F.

^b Post-hoc analysis revealed a difference between 1HR in comparison with 3HR and 6HR. Intergroup comparison revealed a difference between 1HR and 1HR-F and 3HR-F.

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